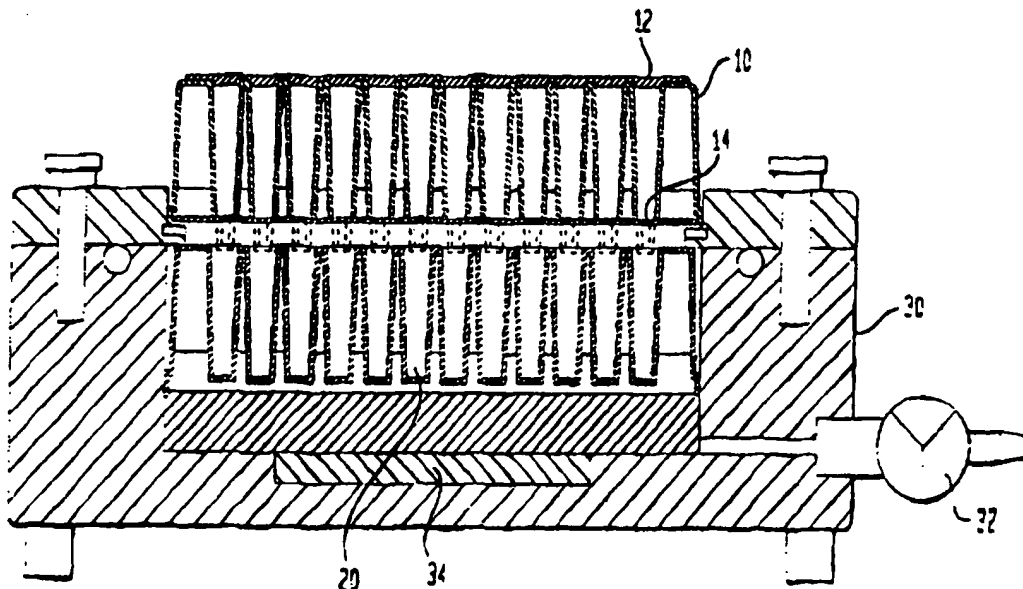




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(54) Title: DEVICE AND METHOD FOR SIMULTANEOUS MULTIPLE CHEMICAL SYNTHESSES



(57) Abstract

The device of the present invention is comprised of a multi-well filter bottom plate (10) with a selectively permeable barrier (14) comprised of a porous substrate having an oleophobic chemical surface. The filter plate (10) is used to contain multiple simultaneous chemical reactions. The selectively permeable barrier (14) holds the reaction mixtures in the wells until such time that it is desirable to remove some or all of the well contents. The selectively permeable barrier (14) is designed or selected to have a lower effective critical surface energy than the surface energy of the reaction mixture. The reaction wells can be drained by lowering the effective surface tension of the reaction mixture; this can be accomplished by altering the surface tension of the reaction mixture with the addition of a surface tension lowering composition. Alternatively, the reaction wells can be drained by the application of a pressure differential across the selectively permeable barrier, or by the application of centrifugal force.

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Title: **DEVICE AND METHOD FOR SIMULTANEOUS
MULTIPLE CHEMICAL SYNTHESSES**

Background of the Invention

Current practice involves the use of multi-well devices with a non-porous base which are not permeable nor can they be easily made permeable. The use of multi-well devices without a porous substrate results in cumbersome and time consuming manipulations (either in a manual mode or an automated mode) since the operator (or instrument) often needs to transfer the contents of the wells (i.e. the reaction medium) to another device (e.g. filtration device) for further processing upon completion of the desired chemical reaction(s). This is particularly inefficient and cumbersome for the formation of desired reaction product(s) which involve multiple or single chemical steps with associated isolation and purification processes as well as syntheses which entail the use of small or minute quantities of reactants and solvents.

Devices with 8 and 96-wells made from porous PTFE (polytetrafluoroethylene) as well as single-well glass devices containing porous PTFE frits or porous glass frits have also been used. Such porous materials have an unfavorable critical surface energy for many of the solvents and reaction conditions typically desirable in chemical syntheses and so do not retain these solutions.

Other devices use a limiting number of multiple, glass cylindrical reaction vessels with a porous-glass base. Such apparatus are not readily amenable to large-scale automation

carried out in the device can be of a homogeneous phase, e.g. a single solution or liquid phase, or a heterogeneous phase, e.g. a liquid phase and a solid phase, a liquid phase and a gas phase, two or more immiscible liquid phases, or any combination of solid, liquid and gas phases. The chemical reaction conditions employable with the multi-well device will depend
5 upon the materials of construction of the device as well as the reaction conditions necessary for obtaining the desired product(s) and include but are not limited to: elevated, ambient and low temperatures and pressures; acidic, basic and neutral aqueous and organic solvents; inert and reactive gases.

A novel feature of the device and methodology of the present invention is a
10 selectively permeable barrier encapsulated within the reaction-well device. This acts essentially as a molecular flow control switch. Permeability through the barrier can be selected for or designed through the interplay of energetics between the critical surface energy of a porous substrate(γ_c), the surface tension of the reaction medium(γ_{mix}), and a deliberate change in the surface tension of the reaction medium(γ_{app}) such that the difference
15 in γ_{app} and γ_c provides for or inhibits spontaneous flow of the reaction medium through the permeable barrier. This selectively permeable barrier "holds-up" or retains the reaction mixture in the wells of the multi-well device until such time that it is desirable to remove some or all of its components through the selective barrier. Removal of the reaction medium or components from the reaction medium is accomplished by manipulation of the effective
20 difference between γ_{app} and γ_c or by the application of a pressure differential across the barrier. Methods of manipulating the effective difference in γ_{app} and γ_c include changing reaction medium or reaction conditions.

The present invention allows for a greater number of simultaneous chemical syntheses to be operating at any one time depending upon the array of wells in the multi-well reaction-

The present invention is amenable to automation either by design or by using existing instrumentation and equipment such as that commonly used in the chemical, pharmaceutical, biotech, and related industries.

These and other features of the invention may be more fully understood by reference
5 to the following drawings.

Brief Description of the Drawings

Figure 1 is a sectional-side view of a 96-well device, i.e. a 12 x 8 array of reaction cells, used in the present invention.

10

Description of the Invention

During the course of this description like numbers will be used to identify like elements accordingly to the different figures that illustrate the invention.

As illustrated in figure 1, the device of the present invention includes: (1) A filter
15 plate 10 with one or more reaction wells and a filter plate cover 12. The plate cover may have associated with it a mechanism and means for attachment (integral or separate to the plate cover) of the cover to the filter plate for operation of the device under a variety of reaction conditions such as elevated or lowered temperatures and pressures. The plate cover may have associated with it a mechanism and means of attachment of a gas manifold
20 (integral or separate to the plate cover) for reactions operating under a variety of atmospheres (inert or reactive) such as argon and nitrogen. In another embodiment, the plate cover may have attached to it (integral or separate to the cover) solid-phase synthetic supports (of a similar or differing array to that of the filter plate) that protrude into the volume of the wells of the filter plate for chemical reaction under a variety of reaction conditions. (2) A

seepage through the porous substrate. As such, the oleophobic chemical surface confers selective permeability to the porous substrate. The oleophobic surface of the porous substrate "holds-up" solvents or other solutions in the multi-well device until it is intentionally desirable to remove some or all of the contents of the multi-well device through the porous substrate.

The critical surface energy of the porous material(γ_c) is an empirical parameter characteristic, in part, of the porous substrate. It depends on such factors as the surface energy of the materials of construction of the porous substrate, the nature and degree of the substrate porosity, the morphology of the porous substrate, the nature and volume(V) of liquid intended for the porous substrate to hold up as well as the temperature(T) and duration(t) of liquid exposure. Typically, the temperature and duration of liquid exposure to the porous substrate can be selected to be typical conditions characteristic of many chemical reactions or characteristic of the reaction condition(s) of interest. The critical surface energy of the porous substrate can be readily determined by exposing the substrate to some fixed volume of liquid(s) or mixture of liquids of known or determined surface tension. Such liquids could include miscible mixtures of one or more alcohols and water of known or determined surface tension as well as homologous series of hydrocarbons (e.g. pentane, hexane, heptane, octane, etc.) or fluorocarbons, or the like with known or determined surface tension. For example the critical surface tension of a porous substrate that allows flow through or seepage of 5 mL(V) of n-pentane (surface tension at 20 °C = 16.0 dynes/cm) and n-hexane (surface tension at 20 °C = 18.4 dynes/cm) over a period of 4 hours (t = 4 hrs.) at 20 °C (T = 20 °C) but, holds-up or provides a barrier towards n-heptane (surface tension at 20 °C = 20.1 dynes/cm) and n-octane (surface tension at 20 °C = 21.6 dynes/cm) under identical conditions would be: $18.4 \leq \gamma_c \leq 20.1$ (in dynes/cm at T = 20 °C, V = 5 mL and t = 4 hrs.)

porous substrate. This increase in the surface tension of the reaction medium may be accomplished by changes in the reaction conditions such as temperature or by the addition of another component, preferably inert to the desired reaction, to the reaction medium that increases γ_{app} , e.g. a solvent with high surface tension, an additive such as a salt or the like.

- 5 (3) Adding an immiscible liquid (immiscible under the desired reaction conditions and, if necessary or desirable, inert to the reaction conditions) with a relatively high surface tension(γ_i) and density greater than that of the reaction medium such that it provides for an intermediate barrier between the porous substrate and the reaction medium. Examples of such immiscible liquids with appropriate characteristics and physical properties would
- 10 include, but are not limited to, water/ether, DMSO/hexane, methylene chloride/water and the like. Those skilled in the art will recognize other binary liquid systems as well as ternary and higher order systems. (4) The application of a net positive partial pressure of an inert gas (inert under the desirable reaction conditions) "downstream" of the porous substrate such that the applied gas is of sufficient pressure to hold-up and prevent flow of the reaction medium
- 15 through the porous substrate.

Low surface energy (or oleophobicity) may be conferred to the porous substrate by a number of different means including, but not limited to, the following: (1) Coating the substrate with oligomeric or polymeric materials with functionality such that the functionality is favorably dispositioned at the solid-liquid interface of the reaction medium and porous

20 substrate. The selection of coating material(s) and associated functionality will depend upon the desirable γ_c . Coating materials include, for example, fluorocarbons and hydrocarbons and the like containing oligomers and polymers. One preferred coating are a combination of perfluoro compounds The oligomeric or polymeric coating may be preformed or prepared in situ. The coating may be cross-linked by thermal, chemical, or radiational techniques

pressure "upstream" of the porous material or by eliminating any net applied partial pressure, or by applying centrifugal force either by use of a centrifuge or other suitable instrumentation.

The lowering of the surface tension of the reaction medium, (γ_{app}) may be accomplished by changes in the reaction conditions such as temperature, or by the addition of another component (inert to the desired reaction) to the reaction medium that lowers γ_{mix} (e.g. a solvent with low surface tension or the like, an additive such as a salt or surfactant or the like which lowers the surface tension).

Examples

The invention can further be illustrated, but is not to be limited, by the following examples.

Example 1:

A glass fiber filter (GF/F, Whatman, Inc.) was dipped into a Fluorad® solution (3M, ID # FC-722) and allowed to saturate. Excess Fluorad was drained and the filter was air dried. The filter was then cured for 15 minutes at a temperature of 100°C.

The treated filter was incorporated into a polypropylene microplate having 96 wells of 2 mL each. A group of three wells was filled with each of twenty six solvents and the

Example 2.

A glass fiber filter (GF/F, Whatman, Inc.) was dipped into mixture of 40 mL Aversin KFC ® (Henkel Performance Chemicals), 10 mL Repellan HY-N ® (Henkel Performance Chemicals), 0.5 grams citric acid, and water to 1 liter, to saturate it. Excess solution was
5 drained. The filter was then cured for 30 minutes in an oven at a temperature of 130°C.

Example 3:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, 1.0 mL methylene chloride was added to each of twelve wells. No liquid drained from the
10 wells after two hours at room temperature.

Multiple additions of 0.2 mL pentane were made to 6 of the wells, followed by mixing and a five minute period to observe any leakage. Slow drainage began only after the third addition (a total of 0.6 mL pentane added to 1.0 mL methylene chloride.

15 Example 4:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, 1.0 mL methylene chloride was added to each of twelve wells.

Pentane (1.0 mL) was added to each of three of the wells. Dripping began within 15 seconds and all the liquid (2 mL) had drained within 75 minutes. No liquid drained from the
20 wells containing only methylene chloride after four hours.

Example 5:

Using a 96 well plate containing a treated glass fiber filter prepared as in Example 2, pentane was added to a dry well. The well was completely drained within ten Minutes.

not drip after 1 hour. Acetone (0.4 mL) was added to the water layer in one well and the well contents were mixed. This well began to drip within 10 minutes. The remaining well containing water and pentane was drained by vacuum.

- 5 While the invention has been described with reference to the preferred embodiment thereof, it will be appreciated by those of ordinary skill in the art that modifications can be made to the structure and form of the invention without departing from the spirit and scope thereof.

Claim 7. A method for performing chemical reactions in a reaction mixture comprising one or more reactants in the reaction-well device of claim 1 comprising the steps of:

a) filling said one or more wells of said reaction-well device with the reaction mixture, wherein the surface tension of the reaction mixture is sufficiently higher than the critical surface energy of the selectively permeable barrier of said reaction-well device to inhibit flow of said reaction mixture out of said one or more wells;

b) draining said one or more wells.

Claim 8. The method of claim 7 wherein the draining of step b) is achieved by lowering the surface tension of the reaction mixture.

Claim 9. The method of claim 8 wherein the surface tension of the reaction mixture is lowered by the addition of an other reactant.

Claim 10. The method of claim 9 wherein said other reactant is selected from the group consisting of a solvent, a salt, and a surfactant.

Claim 11. The method of claim 8 wherein the surface tension of said reaction mixture is lowered by the alteration of reaction conditions.

Claim 12. The method of claim 11 wherein the surface tension of said reaction mixture is lowered by the alteration of temperature.

Claim 18. The method of claim 17 wherein said other reactant is selected from the group consisting of a solvent, a salt, and a surfactant.

Claim 19. The method of claim 15 wherein the surface tension of said reaction
5 mixture is lowered by the alteration of reaction conditions.

Claim 20. The method of claim 19 wherein the surface tension of said reaction
mixture is lowered by the alteration of temperature.
wherein, the draining of step b) is achieved by lowering the surface tension of the liquid
10 barrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/18046

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :B01L 11/00

US CL :422/101

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/58, 68.1, 101, 102, 104; 435/39, 287, 292, 311; 436/177, 809

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 5,219,528 A (CLARK) 15 June 1993, see entire document.	1-3,7 ----- 4-6,8-20
X ----- Y	US 5,141,719 A (FERNWOOD et al) 25 August 1992, see entire document.	1-3,7 ----- 4-6,8-20
X ----- Y	US 5,108,704 A (BOWERS et al) 28 April 1992, see entire document.	1-3,7 ----- 4-6,8-20
X ----- Y	US 5,039,493 A (OPRANDY) 13 August 1991, see entire document.	1-3,7 ----- 4-6,8-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

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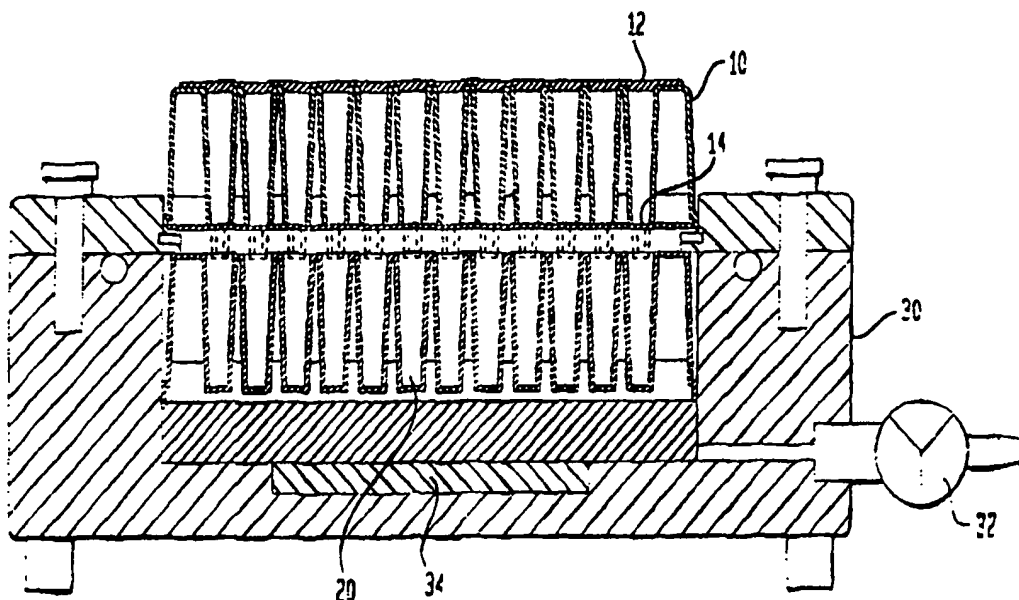
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(54) Title: DEVICE AND METHOD FOR SIMULTANEOUS MULTIPLE CHEMICAL SYNTHESSES



(57) Abstract

The device of the present invention is comprised of a multi-well filter bottom plate (10) with a selectively permeable barrier (14) comprised of a porous substrate having an oleophobic chemical surface. The filter plate (10) is used to contain multiple simultaneous chemical reactions. The selectively permeable barrier (14) holds the reaction mixtures in the wells until such time that it is desirable to remove some or all of the well contents. The selectively permeable barrier (14) is designed or selected to have a lower effective critical surface energy than the surface energy of the reaction mixture. The reaction wells can be drained by lowering the effective surface tension of the reaction mixture; this can be accomplished by altering the surface tension of the reaction mixture with the addition of a surface tension lowering composition. Alternatively, the reaction wells can be drained by the application of a pressure differential across the selectively permeable barrier, or by the application of centrifugal force.

AMENDED CLAIMS

[received by the International Bureau on 25 March 1998 (25.03.98);
original claims 2, 4, 6, 15, 19 and 20 amended; remaining claims unchanged (4 pages)]

Claim 1. A reaction-well device comprising a filter plate having one or more wells and a base comprised of a selectively permeable barrier.

5

Claim 2. The reaction-well device of claim 1 wherein said selectively permeable barrier is comprised of a porous substrate having a [an] low energy surface.

Claim 3. The reaction-well device of claim 2 wherein said porous
10 substrate is selected from the group consisting of glass fiber filters GF/x where x= A, B, C, D, and F (designating different porosities), polypropylene, nylon, PTFE, PVDF, and cellulose.

Claim 4. The reaction-well device of claim 2 [1] wherein said low energy
15 surface is comprised of a coating applied to said porous substrate.

Claim 5. The reaction-well device of claim 4 wherein said low energy surface coating is selected from the group consisting of fluorocarbons and hydrocarbons containing oligomers and polymers.

20

Claim 6. The reaction-well device of claim 2 [1] wherein said low energy surface is comprised of a covalent modification of said porous substrate.

Claim 13. The method of claim 7 wherein the draining of step b) is achieved by the application of a pressure differential across said selectively permeable barrier.

5 Claim 14. The method of claim 7 wherein the draining of step b) is achieved by the application of centrifugal force.

Claim 15. A method for performing chemical reactions in a reaction mixture comprising one or more reactants in the reaction-well device of claim 1
10 comprising the steps of:

1) placing a liquid which is immiscible with said reaction mixture in said one or more wells in a sufficient quantity to form a liquid barrier between said selectively permeable barrier and said reaction mixture;

2) filling said one or more wells of said reaction-well device with the reaction
15 mixture, wherein the flow of said reaction mixture out of said one or more wells is inhibited by said immiscible liquid barrier;

3) draining said one or more wells.

Claim 16. The method of claim 15 wherein the draining of step 3) is
20 achieved by lowering the surface tension of said immiscible liquid barrier.

Claim 17. The method of claim 16 wherein the surface tension of said immiscible liquid barrier is lowered by the addition of an other reactant